In addition, please add claim 47 as follows.

47. (new) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass according to claim 24, wherein before crystallizing, the inhibitor is dissolved in said organic solvents at a temperature of between about 18 to 25°C.

REMARKS

As discussed in the telephone interview, applicants request that the drawings included as part of the international PCT application be accepted as an official part of the specifications in the U.S. national phase application.

Claims Rejections - 35 USC § 112 - Indefiniteness

The Examiner rejected Claims 24-46 under paragraph 2 of §112 as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (See p. 2, 6th paragraph.)

Claims 24, 36, 37, 40, 44 and 45 have been amended to avoid use of the terms "limited solubility or miscibility" and "water-soluble organic solvent," which have been replaced with the term "organic solvent." Support for the substitution is found in the application on p. 7, lines 8-12. Similarly, claims 24 and 40 have been amended to replace the term "water-miscible or water-soluble organic solvent" with just "water-*miscible* organic solvent."

In addition, to clarify the importance of performing the crystallization steps at mild temperatures, claim 24 has been amended to add the term "wherein before crystallizing, the inhibitor is dissolved in said organic solvents at a temperature of

between about 10 to 40°C" as a descriptor of the crystallization steps. Support for this term can be found in the original application on p. 4, lines 3 - 6.

In light of the above amendments, it is respectfully submitted that the claims are no longer indefinite under §112, par. 2 and are thus in a condition for allowance.

Claim Rejections - 35 USC § 102 (b)

The Examiner rejected claims 40-42 under 35 USC § 102(b) as being "clearly anticipated by US 4,319,039 [AB]." (See p.3, second paragraph.)

Applicant acknowledges that U.S. Pat. No. 4,319,039 by Albers-Schonberg (the Albers-Schonberg patent) does disclose a method for ultimately purifying the HMG-CoA reductase inhibitors, either as lactones or as ammonium salts of the acid form, from the fermentation broth by crystallization to a purity of either greater than or equal to 99%. As the Examiner points out ".... the term greater than or equal to 90% [sic – it should be 99%] purity .... is within applicant's claimed range." However, the Albers-Schonberg purification method does not disclose purification of an HMG-CoA reductase inhibitor directly from the fermentation broth using at least two crystallization steps from water-soluble and limited-solubility organic solvents at neutral pH. Depending on the ultimate form of the inhibitor to be purified, the methods disclosed in the Albers-Schonberg patent involve either a single crystallization from a basic mixture of a water-insoluble organic solvent (the ammonium salt form of the inhibitor), or multiple crystallizations using first a basic mixture of a water-insoluble organic solvent and second, a basic mixture of a limited-solubility organic solvents (the lactone form).

Further, the crystallization steps for either the ammonium salt form or the lactone form do not disclose the method of the present invention. For purification of the ammonium salt, the Albers-Schonberg patent discloses two methods. One involves a single crystallization step from either an 80:20:2 mixture of chloroform, methanol and concentrated aqueous ammonium hydroxide, or from toluene at reflux (i.e. boiling) temperatures. The boiling point for toluene is 111° C (*The Systematic Identification of Organic Compounds*, 6th Edition, (1980) p. 556, R. L. Shriner et al., John Wiley & Sons, New York). Neither chloroform nor toluene is a water-miscible organic solvent, nor is the toluene dissolved using mild temperatures between about 10 to 40° C. Further, this method involves a single crystallization step, not two crystallizations.

The other purification method disclosed in the Albers-Schonberg patent does involve two crystallization steps starting from crude lactone and converting to the ammonium salt. The first crystallization is from an 80:20:2 mixture of chloroform, methanol and concentrated ammonium hydroxide, and the second crystallization is from hot isopropanol containing 5% concentrated ammonium hydroxide, further replenished with ammonia gas upon cooling. Although the Albers-Schonberg patent does not define the temperature of "hot" isopropanol, it is presumably not as hot as boiling (83° C, Id. p. 535) but hotter than "warm", generally taken to be about body temperature (37 ° C), just slightly cooler than the upper temperature limit for the present invention, 40° C.

In contrast, the present invention purifies the inhibitor, either as the lactone or the acid, directly from the fermentation broth to greater than 99.6% purity, using essentially just two crystallization steps. More importantly, the purification method of the present invention requires the two crystallization steps be performed with a water soluble organic

solvent and an organic solvent and that the inhibitor be dissolved in the organic solvents for both steps at temperatures between about 10 to 40° C. Neither high temperatures (i.e. reflux conditions) nor concentrated ammonium hydroxide (i.e. high pH) are used in either crystallization step. As such, the purification method of the present invention is novel and not anticipated or disclosed by the Albers-Schonberg patent.

Further, the present purification method was developed after "an extensive study of the chemical compounds produced during the fermentation using different species of microorganisms.... their chemical properties and their behavior in the different solvents at different pH ...." (See application, p. 2, lines 23-28.) Thus, it would not be obvious to one of ordinary skill in the art to predict the purification method of the present invention in advance – one which involves two crystallization steps utilizing two different organic solvent types under mild conditions and which results in purification of a single compound – even in light of the purification methods disclosed by the Albers-Schonberg patent.

CONCLUSION

Claims 24, 36 37, 40, 44 and 45 have been amended to eliminate the indefinite terms. Specifically, the term "limited-miscibility organic solvent" has been replaced with simply "organic solvent," for which there is support in the specifications on p. 7, lines 8-12. In addition, a temperature range for dissolving the inhibitor in the two crystallization steps has been added to claim 24.

The purification method of the present invention was developed after extensive experimentation, and differs substantially from the methods disclosed in the Albers-

Schonberg patent. The Albers-Schonberg patent discloses the preliminary purification of a crude ammonium salt of the HMG-CoA reductase inhibitors, followed by a single crystallization involving a water-insoluble organic solvent at basic pH or reflux temperature. Alternatively, the Albers-Schonberg patent discloses a purification method involving two crystallization steps wherein the inhibitor is dissolved in the second organic solvent at high temperature. The present invention does not require the intermediate purification of a crude ammonium salt form of the inhibitor, nor crystallizations where the inhibitor is dissolved in the solvents at basic pH or reflux temperatures, or even at hot temperatures. Rather, the present invention comprises a direct purification from the fermentation broth of either the lactone or acid form of the inhibitor involving at least two crystallization steps – one using a water-miscible organic solvent and the other using an organic solvent – and in both crystallization steps the inhibitor is dissolved in the organic solvent at temperatures between about 10 to 40° C. Therefore, it would not have been obvious to one skilled in the art to arrive at the present invention after reading the Albers-Schonberg patent.

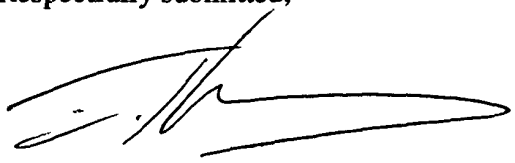
For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

It is believed that no extension of time is needed; however, this conditional petition for an extension of time is being made in the event that the need for an extension has been overlooked. If any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972. The Examiner is

requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Date: January 24, 2002

Respectfully submitted,



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Version with Markings to Show Changes

24. (once amended) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying of the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing [~~crystallization of~~] the HMG-CoA reductase inhibitor from:

i) a water miscible [~~or water-soluble~~] organic solvent; and

ii) [~~crystallization of the HMG-CoA reductase inhibitor from~~] an organic solvent. [~~having limited miscibility or solubility with water.~~],

wherein before crystallizing, the inhibitor is dissolved in said organic solvents at a temperature of between about 10 to 40°C.

36. (once amended) The process according to claim 24, wherein the crystallization step from an organic solvent [~~having limited miscibility or solubility with water~~] comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 [~~g/l~~] g/L, and removing one-third to three-fourth of said organic solvent.

40. (once amended) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined

crystallization steps, which comprise[~~s~~] crystallization from a [~~an~~] water-miscible [~~or water-soluble~~] organic solvent and crystallization from an organic solvent [~~having limited miscibility or solubility with water~~] as final [~~polishing~~] steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.

44. (once amended) The process according to claim 40, wherein said crystallization from an organic solvent [~~having limited miscibility or solubility with water~~]comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 [~~g/l~~] g/L, and removing one-third to three-fourth of said organic solvent.

45. (once amended) The process according to claim 40, wherein ethyl acetate is used as the organic solvent [~~having limited miscibility or solubility with water~~].

47. (new) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass according to claim 24, wherein before crystallizing, the inhibitor is dissolved in said organic solvents at a temperature of between about 18 to 25°C.